CAFFEINE SODIOBENZOATE, SODIUM ISO-AMYLETHYL BARBITURATE, SODIUM BROMIDE AND CHLORAL HYDRATE

EFFECT ON THE HIGHEST INTEGRATIVE FUNCTIONS

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The purpose of this communication is to present a description of the effects of caffeine sodiobenzoate, sodium iso-amylethyl barbiturate, sodium bromide and chloral hydrate on the highest integrative functions. The acquired or conditioned response has been taken as an expression of these functions. For experimental purposes standard methods of testing have been adopted and a measurable component of the conditioned response quantitatively studied. The effects of the aforementioned agents have been compared with other factors that alter responses involving the highest integrative functions.

Animals with a relatively well developed cerebral cortex are characterized as a group by their ability to effect temporary connections between their constantly changing external environment and various activities of their physiologic households. In the broadest terms, it may be said of the group that if there is a coincidence in time of any external stimulus with some activity of the organism, this activity may subsequently be evoked by that external stimulus.

In other words, such animals have the ability to react in a special way to a variety of stimuli, in themselves biologically inconsequential, when these stimuli have been previously coupled directly or indirectly with the occurrence of some biologically significant experience. Such experiences include any act remotely or immediately involved in processes like feeding, reproduction and self-preservation. Moreover, these temporary and unitary reactions are elicited by and dependent on the stimulus, and they depend to a greater extent and far more than any other type of reaction on the conditions existing at the time the stimulus is presented. Thus, a stimulus which under one set of circumstances elicits one reaction may under other conditions evoke the opposite response.

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Should the coincidence of the inconsequential stimulus and significant biologic activity occur often enough and the conditions of the association remain otherwise constant, the reaction may become so regular and predictable as to justify its use as a means of measuring the most complex function for the adjustment of the organism to its environment.

By virtue of this ability the animal develops and readily utilizes new, acquired, individual or nongeneric reactions, as contrasted to old, inborn or species reactions. Any of these adjectives may suitably be affixed to the reaction, but Pavlov, most impressed by their dependence on many conditions, both in formation and in perpetuation, attached to them the adjective "conditioned." He emphasized that it is in their "conditionality" that these reactions contrast most sharply with more stable, older, inborn or species reactions which, as a group, he called "unconditioned."

The fluidity of the conditioned response is further revealed by the fact that when the conditioned stimulus on which it is based fails to be linked with the stimulus which evokes the unconditioned reaction, the response, which may until that time have been regular enough to be predicted, now gradually falls off and eventually, if coupling does not take place again, entirely disappears.

For the formation of a conditioned response three factors are essential: 1. The animal must have a cerebral cortex. 2. The receptor end-organs, the afferent pathways and the efferent apparatus must be intact. 3. A hitherto inconsequential stimulus must precede and overlap in time the presentation of a second stimulus which elicits an inborn reflex.

The unconditioned responses involving glandular activity are especially useful for experimental purposes, and of these, because of technical convenience, the salivary reflex has most often been chosen. The salivary reflex to food is an old, established, relatively fixed and stable reflex which is elicited by stimulating the mucous membranes of the mouth with various nutritive or rejectable substances. For example, when the giving of food is preceded by the ringing of a bell, this previously inconsequential stimulus takes on the character of a symbol or signal, and after several repetitions in combination with the food (now the significant biologic object which evokes the inborn reaction) gives rise to responses which differ only quantitatively from those resulting from the food itself.

The procedure of giving the second stimulus which evokes the unconditioned response is referred to as reenforcement, since it supports or substantiates the delicate and dependent conditioned response. Thus, in the case of the conditioned stimulus just mentioned, the bell is said to be reenforced when it is coupled with food and, conversely, to be nonreenforced when not thus coupled.

In addition to a reaction to a reenforced conditioned stimulus, a reaction of differentiation may be developed. This reaction results from the ability to distinguish between stimuli which often resemble one another closely yet differ in that one is accompanied by the unconditioned stimulus (which evokes the unconditioned response) while the other is not.

A conditioned stimulus which regularly produces a response gradually fails to do so when it is no longer reenforced. Such a conditioned response is said to have become extinguished. However, although the stimuli fail to elicit the type of response that follows reenforcement, they are not without effect on the behavior of the organism. Thus, when produced just before or with reenforced conditioned stimuli which regularly evoke responses, the latter fail to evoke any response or their influence is much reduced. These nonreenforced stimuli have consequently been referred to as negative conditioned stimuli.

Although the disturbance set up by this type of nonreenforced stimulus is superficially less effective, it is highly active in the sense in which a brake applied to a revolving wheel is "active." The contrasting reactions produced by stimuli followed by an unconditioned stimulus and by stimuli not followed by an unconditioned stimulus may be expressed as opposites in the behavior of the animal. Either type can be significant to the animal's adaptability in nature, the former by increasing the reactivity of the organism, the latter by decreasing it.

It may be inferred that a function which enables an animal to sustain or protect itself because it can anticipate significant biologic events by reacting to symbols or signals formed by previously inconsequential stimuli must inevitably influence all the other functions. Its importance becomes evident when it is appreciated that every unconditioned reaction (inborn reflex) may become coupled with some external stimulus which may then determine its check or release. On the other hand, it does not follow that inborn responses are always dominated by the newer function; although strongly influenced, they still maintain their independence.

In other words, the conditioned response through its influence on all other responses of the organism makes possible its adjustment to an ever-changing environment in which the same stimulus takes on at different times an entirely different significance. The inborn reactions may still occur independently, however, as shown by the extension of the leg that follows the sudden stretching of the patellar tendon (knee jerk) in the intact animal. The independent action may be at times to the advantage of the animal and at other times to its disadvantage. It is apparent that conditioned stimuli do not always evoke a response which exerts an "inhibiting" effect on the inborn response; they incite to greater activity as well as hold in check.

The quality of responding to the signals, signs or symbols presented by numerous stimuli which have been substituted for a significant biologic experience may be looked on as the unique expression of the highest type of integrative function. This quality, termed "signalization" (Pavlov) or "symbolization" (A. Meyer), is the common denominator of all conditioned responses, which may differ enormously in complexity and range, depending on the experience and structural equipment of the animal form investigated.

On these fundamental observations and conclusions the experiments presented in this paper were based. The conditioned response was taken as an expression and test object of the highest integrative function, and the defining qualities just briefly reviewed may be summarized as follows: 1. The conditioned response is the reaction which occurs during the period in which only the symbol is present and before the giving of the stimulus which sets off the inborn or species reflex. 2. It may become weak or disappear should the symbol no longer be coupled with food or with any other stimulus eliciting an inborn reflex. 3. In contrast to the positive type of response, a reaction of differentiation may be developed. This differentiation may be defined as the ability to distinguish between symbols which, although perhaps closely resembling the positive, differ essentially in that they are not accompanied by the stimulus which sets off the inborn or species reflex. 4. These higher integrative functions exert a significant influence on the lower integrative functions.

METHOD

The method used was that developed by Pavlov for the study of conditioned responses. The details of the method of salivary transmission, recording and production of stimuli were modified in an attempt to attain more constant readings and to reduce the errors.

Dogs were used in the experiments. A salivary fistula was produced on each dog's left cheek by dissecting the ampulla of Stenson's duct and everting it so that it drained on the outside of the cheek. Thus all the saliva produced in one parotid gland could be collected by placing a glass cup over the outlet of the duct. Such a glass cup was connected by means of rubber and copper tubing to a manometer about 2 meters distant and situated outside the chamber in which the dog stood during the experiment. The entire conduction system was filled with water, and near the dog was a salivary reservoir which collected most of the saliva and prevented clogging of the copper tubing.

The animal was placed in a chamber constructed in such a way that the experimenter was able to control the environmental circumstances. It was in principle a sound-proof compartment with an inner chamber, measuring 2 by 2 by 2 meters, and with walls 30 cm. thick. In this manner the light, temperature, sound and touch were largely controlled by the experimenter. The animal stood on a platform in front of an automatic food box so built that the experimenter could at a desired moment present a standard article of food to the dog.

The animal was tied by a strap from its collar but was otherwise not bound or supported except in the experiment with drugs. The feet and body were free to move about, but the dog could not get out of the operator's field of vision because of the light leash.

On the wall of the inner chamber were buzzers, metronomes, lights, etc., used as signals; all these signals were controlled from the operator's keyboard.

A small aperture in the wall made it possible to observe the animal during the period before and after the stimulation. The salivary production was measured directly by a manometer and recorded by means of an electric drop recorder. The use of tape and markers made possible a complete graphic record of the time when the stimulus was begun, the amount of saliva produced before the food was presented, the amount present when the food was given and, if desired, the amount produced after the food had been given.

The conditional response to the bell was developed as follows: The dog was placed in the chamber, and after a short period the bell was sounded and allowed to ring for ten seconds. At the end of that time the food was automatically presented in front of the dog. The bell continued to ring without interruption for another twenty seconds, ringing thirty seconds in all. This procedure was repeated again and again; the bell sounded at from four to five minute intervals and alternated with another stimulus, such as the sound of a metronome beating sixty times per minute or a bubbling sound; all the sounds were accompanied by the presentation of food. Generally after from ten to twenty repetitions there was a secretion of saliva as soon as the bell started to ring and before the food was given. After twenty or more repetitions the response became relatively constant. In this manner conditioned responses to the stimulus of a bell, a bubbling sound, the sound of a metronome beating 60 times per minute and a light were developed.

When moderately large and constant responses to these stimuli were being obtained a differentiation was developed by introducing as a stimulus the sound of a metronome beating 140 times per minute, as contrasted to the sound of one beating 60 times, which was always coupled with presentation of food. The sound of the metronome with 140 beats per minute was never coupled with presentation of food. At first the response to this new, nonreenforced stimulus was the same as that to the stimulus coupled with the offering of food, but after about forty presentations of the stimulus without food the stimulus no longer elicited the salivary flow. The nature of this type of reaction is dicussed later.

The experiments were performed at approximately the same hour daily, Sundays excepted. The animals were fed and exercised at about the same time, and the conditions outside the experimental chamber were kept as nearly constant as possible.

Attention is called to the error of ± 15 cu. mm. in the measurement of the saliva; it was due chiefly to the movement of the column of fluid in the manometer resulting from the movement of the dog's head.

EXPERIMENTAL ANIMALS

The experiments were performed on two dogs. Since the type of animal is a factor in the response under any given set of circumstances, a few words of description are necessary to a proper evaluation of the observations.

The first dog (Kompa) was a long-nosed, large-pawed female mongrel of the yellow, short-haired variety, resembling a bloodhound, and weighing 25 Kg. It

was restless, active, capricious, friendly and highly investigative. It barked a little at times, and although seldom aggressive in seeking a quarrel, it fought vigorously when attacked. Positive conditioned reactions were readily developed, and the response was fairly constant. Differentiation was not as easily elaborated, but when ultimately developed it was fairly constant under proper conditions. Under unusual activity, hunger or illness of any variety it became imperfect. In the chamber during the preexperimental period the animal commonly remained standing quietly upright on all fours with the eyes wide open and the head erect. At the beginning of each experiment it usually jumped on the platform with great alacrity. A striking feature was the apparent inability of this animal to develop complete differentiation without immediately going to sleep. The "sleep" was usually of short duration and did not interfere with the progress of the experiments.

With the exception of two months in 1930, the dog remained in the experiment for two years without showing any failure in the intensity or constancy of the response. Such variations as did occur were induced by the operator or by transient illness. All the tables included in this report are taken from protocols on this dog.

The second dog (Curley) was a gray, long-haired male mongrel of the spaniel variety, weighing about 10 Kg. It was active, lively and friendly and barked considerably during activity. It avoided quarrels and usually retreated from engagement when attacked. Acquired reactions were readily developed and remained fairly constant. Differentiation was not attempted. For the purpose of these experiments this dog was not completely satisfactory because the parotid saliva measured was but a small fraction of the total saliva produced. Although the absolute amount was constant it was so small that the error of the method became disproportionately great. Therefore, while the observations on this animal were useful in relation to those on the first dog, they were never accepted as conclusive. It is, however, interesting to note that the results of the experiment on the two dogs differed in quantitative aspects only.

OBSERVATIONS

Control Experiments.—In order to determine the effect of the chemical substances used a series of average control responses were first developed. In the manner described, conditioned responses to the following stimuli were elaborated: the ringing of a bell, a bubbling sound made by passing a stream of air through a bottle of water near the dog's head, the sound of a metronome with 60 beats per minute and a light flashing at a frequency of 60 flashes per minute. In each case the stimulation preceded by ten seconds the presentation of food and continued for twenty seconds during and after the latter procedure. As a differentiated stimulus a metronome beating with a frequency of 140 per minute and never coupled with food was used, and the sounding was continued for sixty seconds. In this instance the readings were made at the end of each period of ten seconds during the sixty seconds in which the metronome sounded.

After many repetitions of the stimuli independently and in changing combinations, a given combination of stimuli was selected. Thereafter the stimuli always followed each other in a definite sequence. The order was: bell, metronome (140 beats per minute), bubbling sound, metronome (60 beats per minute), flashing light and the bell again. This pattern was repeated ninety-one times. At first there were marked fluctuations in the magnitude of the responses, but on further repetition the response became more constant. The average response to the various stimuli was based on from thirty-one to fifty relatively stable responses.

The responses for the control period are shown in table 1. The bell and the bubbling sound elicited a greater response (222 and 231 cu. mm.) than did the other two stimuli. The sound of the metronome with 60 beats per minute produced a response next in order of strength (189 cu. mm.), and the flashing light was the weakest of the reenforced stimuli, producing a secretion of 151 cu. mm. of saliva. The sound of a metronome with 140 beats per minute usually elicited little or no salivary response.

In approximately from 69 to 87 per cent of the repetitions the responses associated with the reenforced stimuli fell within a range of 110 cu. mm. In about from 73 to 79 per cent of the repetitions the nonreenforced stimulus elicited a response of less than 15 cu. mm. From 13 to 31 per cent of the responses were outside of the limits mentioned. The distribution is graphically portrayed. The degree of probability that a given stimulus will elicit a given response can, therefore, be determined from an examination of table 1.

With the reenforced stimuli the general activity as quantitatively approximated by the crude method of observing the animal through the porthole in the experimental chamber roughly paralleled the salivary response.[1] (This is by no means always true.) The average or usual response for the reenforced stimuli was as follows: The dog stood quietly and erect before the food box, usually looking at it or over it. The eyes were well opened, the ears half erect; the animal did not support itself by resting any part of the body on the stand nor did it pull, scratch or jump about on the platform. The breathing was regular and slightly rapid. During the period of stimulation there was a quick turn of the head toward the source of the stimulus (orientation), followed by a turning of the head toward the food box and by a slight step forward with the eyes even more widely opened. The conditioned flow of the saliva usually preceded by several seconds the movement toward the box. When the food was presented, the head quickly bent forward, and the biscuits were rapidly eaten. Then the dog assumed the usual attitude.

The behavior of the dog before the presentation of the nonreenforced stimuli was similar to that described before the presentation of the reenforced stimuli. However, at the sound of the metronome (140 beats, nonreenforced) the head was turned slightly in the direction of the sound and then fell forward, often hanging low, and after from nine to ten seconds it was supported on the box. The eyes were closed, and the animal squatted on its haunches, leaning against the wall and the food box. The breathing was slow and dull. This was called "sleep" because of its resemblance to the condition described by that term and for want of a more objective description and definition of "sleep."

In the observations on the administration of drugs, the action of the drug was determined as follows: The agent was administered, and the responses to the various standard stimuli were determined. These responses were then considered in terms of the probable spontaneous variations under control conditions. If the probability that the response would occur spontaneously was small it was inferred that the unusual reaction resulted from the effects of the drug. In other words, if in a small number of the control observations the animal produced 220 cu. mm. of saliva in response to a standard stimulus whereas after the administration of the drug 340 cu. mm. of saliva was produced much more frequently, this increased secretion could be attributed to the effects of the drug.

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1. The salivary response to the metronome beating 140 times per minute in the control series fell within the limit of error of the apparatus (15 cu. mm.) and is considered negligible in this case.

TABLE 1.—*Summary of Control Experiments* *

Signals	Bell (R)	Metronome (140 beats per minute) (N)	Bubbling sound† (R)	Metronome (60 beats per minute) (R)	Light (flashed 60 times per minute (R)	Metronome (140 beats per minute) (N)	Bell (R)
Total repetitions	238	264	70	138	127	264	238
Total repetitions in combination	91	91	91	91	91	91	91
Total repetitions in stable combination	42	41	31	50	40	44	38
Amount of saliva in cubic millimeters	0- 50= 0= 0% 50-100= 2= 4.8% 100-150= 2= 4.8% 150-200= 9=21.4% ‡200-250=13=31.0% 250-300=12=28.5% 300-350= 4= 9.5% 350-400= 0= 0%	0 =18=44% ‡0- 15=12=29.3% 15- 30= 5=12.2% 30- 50= 4= 9.7% 50- 70= 2= 4.8% 70-400= 0= 0%	0- 50= 0= 0 50-100= 1= 3.2% 100-150= 2= 6.4% 150-200= 6=19.3% ‡200-250=11=35.5% 250-300= 9=29.0% 300-350= 0= 0% 350-400= 0= 0% 400-410= 2= 6.0%	0- 50= 0= 0% 50-100= 3= 6% 100-150= 8=16% ‡150-200=15=30% 200-250=19=38% 250-300= 3= 6% 300-350= 1= 2% 350-400= 1= 2% 400-410= 0= 0%	0- 50= 1= 2.5% 50-100= 1= 2.5% 100-150=18=45.0% ‡150-200=14=35.0% 200-250= 5=12.5% 250-300= 1= 2.5% 300-350= 0= 0% 350-380= 0= 0%	0 =25=48.0% ‡0- 15=14=27.0% 15- 30= 9=17.3% 30- 50= 3= 5.8% 50- 70= 0= 0% 70-110= 1= 1.9% 110-400= 0= 0%	0- 50= 0= 0% 50-100= 0= 0% 100-150= 6=15.8% ‡150-200=14=36.9% 200-250=11=29.0% 250-300= 4=10.5% 300-350= 2= 5.3% 350-400= 1= 2.6%
	‡180-290=29=69%	‡0-15 (incl.)=30=73.3%	‡180-290=24=77%	‡130-260=38=76%	‡100-220=37=92.5%	‡0-15(incl.)=39=75%	‡140-240=27=71.0%
General reaction	++	±S	++	++	+	±S	++
Response in cu.mm. of saliva:							
Minimum response	180	0	180	130	100	0	140
Average response	222	9 (0)	231	189	151	11 (0)	200
Maximum response	290	15	290	250	220	15	240

* In the experiments the experimental error equaled ±15 cubic millimeters; the time interval between stimuli was from four to six minutes; the experiments were performed from 1:30 to 3:00 p.m. The following symbols are used in this and in the following tables: S indicates sleep; ±S denotes a state of lethargy to sleep in which the dog squatted, resting the head on the box; ± denotes drowsiness, a lethargic state with the eyes half shut, the animal leaning against the apparatus; + denotes a quiet attitude, drooping head, open eyes and a standing or squatting posture; ++ indicates that the dog stood erect, with eyes wide open and ears half erect; the posture was upright and the movements were quick; +++ indicates that the dog moved about, was restless and whined; ++++ indicates that the dog was very restless, pulled on the harness or jerked off the apparatus, whined and barked. R indicates reenforced stimuli; N, nonreenforced stimuli.

† The "bubbling sound" was produced by passing air through water.

Before the action of the drug was tried a preliminary control period of several days preceded the experiment, to insure against an error of interpretation due to a temporary and "spontaneous" change in the responses of the animal. The observations made during this period coincided with those obtained in the average and during the longer control period. This "control" gave a stable basis for comparison and, what is more important, furnished a better conception of the range of probability of a given response following the stimulus, so that fewer experiments with drugs were necessary.

It was essential to keep the experiments with drugs at a minimum for the following reasons: 1. Each experiment testing the action of a drug required that the responses be measured repeatedly over many hours. This meant that the animal had to spend from five to seven hours of the twenty-four in the experimental chamber. 2. There was a slight risk to the life of the animal with each intoxication. 3. There was danger that unusual responses would develop as a result of repeated punctures or enemas given just before the animal entered the experimental chamber, and such alterations in responses would complicate the results and make it difficult to interpret the effects of the drug.

TABLE 2.—*Effect of Repeated Determinations at Short and Irregular Intervals* *

Stimulus		Control Average			Experiment of June 26				
		Minimum	Mean	Maximum	2:05 P.M.	8:18 P.M.	9:41 P.M.	11:12 P.M.	General Reaction
Bell	R	180	222	290	182	273	222	271	++
Metronome (140)	N	0	9	15	0	0	0	0	S
Bubbling sound	R	180	231	290	287	255	196	204	++
Metronome (60)	R	130	189	250	209	209	193	169	++
Light (60)	R	100	151	220	164	127	?	118	+
Metronome (140)	N	0	11	15	0	0	0	0	S
Bell	R	140	200	240	238	191	184	173	++

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

As a result of these considerations we adopted the procedure of performing the maximum number of preliminary control experiments compatible with the maintenance of stable responses, and of following these experiments by the minimum number of consistent tests for the action of the substance under consideration.

It was also necessary to control the effect of the repetition of observations, i.e., from five to seven periods of detention in the camera within twenty-four hours. Furthermore, the fact that many of the observations were made late at night—at an hour unusual for the animal—possibly complicated the results. After the experiments with each drug were completed a further series of measurements was made on another day to determine the effect of the procedure. The dog was treated as though a drug was to be administered, and the responses were measured at irregular intervals during the next twenty hours. If the responses were then stable, one could infer that they had not been influenced by the procedure itself.

As is shown in table 2, the salivary production was always within the range of the average, although there was a slight decrease toward the end. It is therefore likely that such alterations in the responses as were observed after the administration of the drug were not due to the extraneous circumstances of the experimental procedure itself.

Experiments with Caffeine Sodiobenzoate.—Control observations on the day preceding the first experiment with caffeine sodiobenzoate showed the conditioned response to be generally lower than usual. This was accepted as satisfactory. Caffeine sodiobenzoate was injected intramuscularly in the amount of 0.016 Gm. per kilogram, or a total of 0.4 Gm. The injection was given after the animal

TABLE 3.—*Observations on the Effect of Caffeine Sodiobenzoate* *

Stimulus		Control Salivary Production: Minimum	Average	Maximum	April 25	General Reaction
Bell	R	180	222	290	218	++
Metronome (140)	N	0	9 (0)	15	0	S
Bubbling sound	R	180	231	290	246	++
Metronome (60)	R	130	189	250	233	++
Light (60)	R	100	151	220	187	+
Metronome (140)	N	0	11 (0)	15	0	S
Bell	R	140	200	240	233	++

April 29, 2:20 p.m. Caffeine Sodiobenzoate, 0.4 Gm. Intramuscularly

Time	Stimulus		Latent Period†: Secretory Response	Latent Period†: Motor Response	Salivary Production	General Reaction
2:28 p.m.	Bell	R	2	3	227	++
2:33	Metronome (140)	N	10	—	27	++
2:38	Bubbling sound	R	2	3	196	++
2:43	Metronome (60)	R	1	2	256	+++
2:48	Light (60)	R	—	—	?	
2:53	Metronome (140)	N	9+	—	73	+++
2:58	Bell	R	1	2	246	+++
3:40	Bell	R	1	2	387	++++
3.45	Metronome (140)	N	10	—	20	++
3:50	Bubbling sound	R	1	2	322	+++
3:55	Metronome (60)	R	2	3	258	+++
4:00	Light (60)	R	1	—	273	+++
4:05	Metronome (140)	R	—	—	9	±
4:10	Bell	N	1	2	265	++
8:10	Bell	R	2	4	209	++
8:15	Metronome (140)	N	10	—	16	±S
8:20	Bubbling sound	R	1	2	364	++++
8:25	Metronome (60)	R	2	9	282	+++
8:30	Light (60)	R	2	—	218	+++
8:35	Metronome (140)	N	10	—	51	+++
8:40	Bell	R	2	4	227	++
	April 30 (20 Hours Later)					
4:05 p.m.	Bell	R	2	3	255	++
4:14	Metronome (140)	N	—	—	0	S
4:19	Bubbling sound	R	3	4	273	+
4:24	Metronome (60)	R	3	4	186	+
4:29	Light (60)	R	4	—	127	+
4:34	Metronome (140)	N	10	—	20	±S
4:39	Bell	R	2	3	206	++
4:44	Metronome (140)	N	—	—	0	S

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

had been prepared for the experiment with head-gear in place so that the first observation could be made a few minutes later.

A protocol has been tabulated (table 3). Immediately after the administration of the caffeine sodiobenzoate, the responses were slightly increased, possibly because of the procedure of injection. At 2:53 p. m., twenty-six minutes after the injection, the response to the metronome (140 beats per minute) was raised to 73 cu. mm. This was the earliest effect of the drug seen in the protocol described, although the metronome beating 60 times per minute just preceding the adminstration of the drug also evoked an increased response. At 3:40, one hour

and thirteen minutes after the injection, the stimuli were repeated. The responses throughout were increased. However, the effect was more apparent in the response to the reenforced stimuli than in that to the nonreenforced stimuli. In fact, during this phase of its action the caffeine sodiobenzoate seemed to improve the differentiation slightly.

The latent period or reaction time, i.e., the time between the presentation of the stimulus and the reaction of salivary secretion and of movement toward the food box, was determined in most experiments. The effects of caffeine sodiobenzoate on the latent period are shown in table 4. The latency is usually shortened. This shortening of the period is more evident during the first two hours following the administration of the caffeine sodiobenzoate and less so six hours later. Table 4 shows that in approximately 80 per cent of the observations the latency of secretion in reaction to the standard stimuli after the administration of caffeine sodiobenzoate occurred in the first two seconds. This contrasts with the 10 per cent that occurred in the first two seconds in the control series. The effect is particularly evident in the case of the stimuli that commonly had a longer latency

TABLE 4.—*Period of Latency Between Stimulation and Response* *

	Before Caffeine Sodiobenzoate				After Caffeine Sodiobenzoate			
	Number of Observations		Percentage of Occurrence		Number of Observations		Percentage of Occurrence	
Time in Seconds	Secretory Response	Motor Response	Secretory Response	Motor Response	Secretory Response	Motor Response	Secretory Response	Motor Response
1	5	0	1.6	0	14	0	42.4	0
2	27	0	8.9	0	13	8	39.4	23.6
3-7	264	155	87.4	57.0	6	17	18.2	50.0
7-10	6	117	1.9	43.0	0	9	0	26.4
Total	302	272			33	34		

* The following stimuli were used: a bell, a bubbling sound, a metronome beating 60 times per minute and a light flashed 60 times per minute.

(flashing light), and is more apparent on the latency of the salivary secretion than on that of the motor reaction. The method of observing the latter is very crude and cannot be accepted too literally. The more subtle movements of the animal toward the food box can hardly be accurately timed. Short reaction time in most instances accompanied an increased secretion of saliva.

Sleep, which usually accompanied the sound of the metronome beating 140 times per minute, was completely dispelled. During the entire period of the experiment the animal was unusually quick in its movements; the head was held somewhat higher; the ears were raised, and the eyes were wide open. Following the stronger stimuli there was considerable restlessness with quasipurposive movements, more rapid breathing and occasional outbursts of panting. As mentioned, the movements of the head both in the initial turning of the head toward the source of the stimulus (orienting movements) and the later movement toward the food box (conditioned movements) were extremely rapid. The only change noted during the sounding of the metronome (140 beats per minute) was a slight lowering of the head and a collapse of the erected ears. Never did the animal rest its head on the box or lean against the supports.

Observations continued to be made every four or five hours after the injection over the next twenty-seven hours and were repeated once each day for the next few days. Six hours after the injection the effect of the drug was still apparent.

At no time was there a decrease in the responses. (As a fact, the values during this period returned to the low level observed just before the caffeine sodiobenzoate was administered.) Sleep with and after the sounding of the metronome at 140 beats per minute recurred about twenty-seven hours after the injection.

During the height of the reaction following the administration of the drug all the salivary responses were increased over 20 per cent, and about half of them were increased to a degree not commonly seen in spontaneous variations from the average (chart 1). The motor activity roughly paralleled the degree of increase in the salivary responses.

Five experiments with caffeine sodiobenzoate were performed. In one experiment, which was carried out during estrus, the animal was restless and overactive. It was observed that the effect of the drug on the response to the nonreenforced

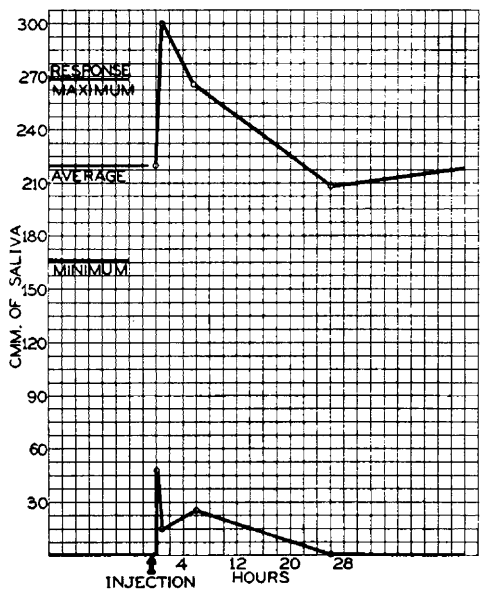

Chart 1.—Composite graphic representation of the effect of caffeine sodiobenzoate. Caffeine sodiobenzoate (0.4 Gm.) was injected intramuscularly (time indicated by the arrow). During the subsequent thirty minutes the responses of the dog to the reenforced conditioned stimuli (bell, bubbling sound, metronome [60 beats per minute] and light [60 flashes per minute]), represented by the upper line, were unchanged from the level for the control period. Beginning then, however, the responses increased. Thus, the response to the nonreenforced stimulus (metronome [140 beats per minute]) represented by the lower line averaged 50 cubic millimeters of saliva, in contrast to the zero response observed during the control period. One hour and twenty minutes after the injection the animal was overalert, active and highly responsive to all conditioned stimuli. At this point the reaction to the metronome beating 140 times per minute was still increased. Measurements made four and one-half hours later showed that the animal gave responses approximating the maximum control level. Twenty hours after the first observation responses to all the stimuli had approached the original level.

stimulus was greater than the effect on the response to the reenforced; the latter response was actually somewhat reduced. This variation may have been related to the initial highly responsive state of the animal. In this instance after the administration of caffeine sodiobenzoate the dog was extremely restless and overactive. With this exception the results in all experiments were similar; sleep was dispelled in all instances.

Experiments with Sodium Iso-Amylethyl Barbiturate.—As in the case of the caffeine sodiobenzoate, the animal was prepared for the measurement of salivary flow before the drug was injected. Small and large doses were given intraperitoneally in a 10 per cent aqueous solution. The first measurement was made as soon thereafter as was technically possible. The large doses induced a prompt and relatively deep narcosis, and the small doses produced a light narcosis or sleep which was of short duration. The action on the conditioned response was investigated for both dosages. A larger dose was given first (table 5). An injection of approximately 30 mg. per kilogram, or a total of 725 mg., was given at 1:58 p. m., and immediately thereafter the animal was lifted in place on the platform. Unfortunately, owing to technical difficulties the first reading could not be made until 2:10 p. m., although during the first two or three minutes after the injection the animal was definitely overactive. By the time the reading was made the animal had become lethargic and showed little response to the usual stimuli. In fact, no salivary responses were obtained until 8:56 p. m., six and three-quarters hours later, although the entire series of stimuli were given at 4:45 and at 6:45 p. m.

From 2:10 until 4:57 p. m. the animal did not take the food, and not even the unconditioned response could be obtained by actually placing the food in its mouth. However, although both the conditioned and the unconditioned reflexes had entirely disappeared, a slight quivering or even a slight elevation of the ears could be detected when the strong sound stimuli were presented. These orienting movements were the last to be submerged and the first to reappear. Sometimes they were strong (in fact more evident than usual) before the conditioned responses had attained any degree of stability and grew weaker as the latter regained their former strength until, with the reestablishment of the conditioned responses, they were of the usual weakness and entirely secondary to the movements associated with the conditioned responses. At 4:57 p. m., nearly four hours before the conditioned response reappeared, the unconditioned response to the food returned and reached its full strength at once.

The conditioned response to the bell (the loudest stimulus) was the first to return and that to the metronome (60 beats per minute) the second. The animal still remained asleep between stimuli, and during and after the sounding of these two stimuli moved just enough to eat the food. Sleep returned at once after the feeding.

At 12:25 a. m., about eleven hours after the injection, responses were obtained to all the test stimuli except to the light. At 3:40 a. m., about fourteen hours after the injection, the bell, the simulus of greatest intensity, which throughout had elicited the greatest responses, caused 382 cu. mm. of saliva to be secreted. This amount far exceeded the "control" level and approximated that elicited by the bell at the height of action of the caffeine sodiobenzoate. The responses to the sound of bubbling and of the metronome (60 beats per minute) at this time, although considerably higher, did not equal the responses to the bell. The determination made twenty-four hours after the injection showed that the general responsiveness was higher than the preexperimental average.

TABLE 5.—*Observations on the Effect of Sodium Iso-Amylethyl Barbiturate* *

Control Salivary Production

Stimulus		Minimum	Average	Maximum	March 11	March 12	March 16	March 17	General Reaction
Bell.....	R	180	222	290	237	287	275	233	Alert
Metronome (140)..	N	0	9 (0)	15	0 (?)	0	0	22	Quiet sleep?
Bubbling sound...	R	180	231	290	136	122	118	175	Alert
Metronome (60)...	R	130	189	250	184	204	127	142	Quiet alert
Light (60).....	R	100	151	220	173	133	109	124	Quiet alert
Metronome (140)..	N	0	11 (0)	15	0	0	0 (?)	0	Sleep
Bell.....	R	140	200	240	178	164	122 (?)	173	Alert

March 19, 1:58 p.m.: Sodium Iso-amylethyl Barbiturate, Intraperitoneally
Dose: 725 Mg. in 10 per Cent Aqueous Solution

Time	Stimulus		Latent Period† Secretory Response	Latent Period† Motor Response	Salivary Response	General Reaction
2:10	Bell.....	R	—	—	0	Slept heavily
2:13	Metronome (140)	N	—	—	0	Slept heavily
2:19	Bubbling sound.	R	—	—	0	Slept heavily
2:20	Metronome (60).	R	—	—	0	Slept heavily
2:24	Light (60).....	R	—	—	0	Slept heavily
2:27	Metronome (140)	N	—	—	0	Slept heavily
3:13	Bell.....	R	—	—	20 (?)	Slept heavily
3:15 to 4:45 p.m. dog asleep						
4:45	Bell.....	R	—	—	0	Slept; did not eat
4:49	Metronome (140)	N	—	—	0	Slept; did not eat
4:57	Bubbling sound.	R	—	—	0	Slept; awakened by bubble; staggered
5:02	Metronome (60).	R	—	—	0	Went to food only when it appeared
5:07	Light (60).....	R	—	—	0	Went to food only when it appeared
5:12	Metronome (140)	N	—	—	0	Slept throughout
5:12 to 6:45 p.m. dog asleep						
6:45	Bell.....	R	—	—	0	Awakened by stimulus
6:49	Metronome (140)	N	—	—	0	Head on box; unsteady hindlegs; slept
6:54	Bubbling sound.	R	—	—	0	Awakened by stimulus; ate; hung head
6:59	Metronome (60).	R	—	—	0	Awakened by stimulus; ate; hung head
6:59 to 7:11 p.m. dog asleep						
7:11	Bell.....	R	—	—	0	Awakened by stimulus but unsteady on legs; slept
7:16	Metronome (140)	N	—	—	0	Slept
7:21	Light (60).....	R				Awakened by stimulus; did not eat; slept
7:21 to 8:56 p.m. dog asleep						
8:56	Bell.....	R	7	—	82	Slept heavily
9:01	Metronome (140)	N	—	—	0	Slept heavily
9:05	Bubbling sound.	R	—	—	0	Slept heavily
9:10	Metronome (60).	R	9	—	27	Slept heavily
9:15	Light (60).....	R	—	—	0	Slept heavily
9:25	Metronome (140)	N	—	—	0	Slept heavily
9:30	Bell.....	R				Slept heavily
A.M. March 20						
12:25	Bell.....	R	6	—	200	Alert
12:30	Metronome (140)	N	—	—	0 (9)	Slept
12:35	Bubbling sound.	R	8	—	82	Slept; awakened by stimulus; ate; slept
12:40	Metronome (60).	R	7	—	113	Slept; awakened by stimulus; ate; slept
12:45	Light (60).....	R	—	—	0	Slept; awakened by stimulus; ate; slept
12:50	Metronome (140)	N	—	—	0	Slept
12:55	Bell.....	R	—	—	0	Slept; awakened by stimulus; ate; slept
3:40	Bell.....	R	2	4	382	Alert; overactive; restless
3:45	Metronome (140)	N	—	—	0	Slept
3:50	Bubbling sound.	R	3	5	169	Slept; awakened by stimulus; ate; slept
3:55	Metronome (60).	R	4	4	127	Slept; awakened by stimulus; ate; slept
4:00	Light (60).....	R	—	—	0	Slept
4:05	Metronome (140)	N	—	—	0	Slept
4:10	Bell.....	R	—	—	0	Slept
P.M. March 20						
1:12	Bell.....	R	5	5	307	Alert; did not sleep; overactive
1:17	Metronome (140)	N	—	—	—?	Slept
1:21	Bubbling sound.	R	2	1	318	Alert; overactive
1:26	Metronome (60).	R	5	—	184	Alert; overactive
1:30	Light (60).....	R	6	5	93	Alert; overactive
1:35	Metronome (140)	N	—	—	0	Slept
P.M. March 21						
1:36	Bell.....	R	3	4	282	Alert; overactive
1:57	Bell.....	R	3	4	227	Erect; quiet; quick movements
2:02	Metronome (140)	N	—	—	0	Slept
2:16	Bubbling sound.	R	4	6	173	Erect; quiet; quick movements
2:21	Metronome (60).	R	3	6	318	Erect; quiet; quick movements
2:26	Light (60).....	R	?	?	173	Erect; quiet; quick movements

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

The general activity roughly paralleled the salivary responses. The dog was awake and moderately active at 12:25 a. m., but with the sounding of the bell slept soon after the food had been given and thereafter awoke only with the sound of the bubbling and metronome (60 beats per minute). When the sound ceased it immediately went to sleep again. The situation differed when the metronome beating 140 times per minute was sounded. Each time this stimulus was introduced the animal, if leaning against the box, sagged even more and if standing erect fell against the supports; if the eyes were half open they closed after four seconds, and the animal went into a sleep from which it did not awake until either the bubbling or the bell was sounded again.

At 3:40 a. m. (fourteen hours after the administration of the drug) the new phase began. The animal moved excessively; the salivary response after the bell was greatly increased, the ears were erect; the dog maintained an erect posture; the breathing was rapid, and panting occurred for a minute. This overactive state did not last very long, for with the sounding of the metronome (140 beats per minute) the dog slept again. Ten hours later, or twenty-four hours after the beginning of the experiment, the animal was in a state of overactivity practically all the time except during and after the sounding of the metronome beating 140 times per minute. This sound was always followed by a light, interrupted sleep (table 5).

A dose about half the size of the preceding, namely, 15 mg. per kilogram, or a total of 375 mg., was injected intraperitoneally in two experiments (table 6). In both instances measurements of the responses were quickly obtained before narcosis occurred. The bell evoked a salivary production of 382 cu. mm., similar to that obtained in the first experiment during overactivity following the narcotic phase. This was followed by a loss of all acquired responses; at 2:13 p. m. the response to the metronome beating 140 times per minute was actually greater than that to the bell or the bubbling sound. Withing an hour and a half, however, the responses returned, and their return was in the order of the intensity of the stimuli, the response to the bell and the bubbling sound returning first, that to the metronome next, and that to the light last. In this experiment, as in the first, the reenforced stimulus (metronome, 140 beats per minute) augmented such soporific qualities as were already present. With the small dose the unconditional or inborn reflex was never lost. Furthermore, the secondary increase in responses following the narcotic phase was not observed. As in the first experiment, the orienting movements were stronger during the stage in which the conditioned responses were reduced and grew weaker as the conditioned responses again attained their former magnitude.

After the initial activity, characterized by pulling on the supports,[2] putting the feet on the food box, swinging the head about, treading from one side of the platform to the other and responding with great speed to the sound of the bell, the animal gradually became more and more unsteady on its feet, sat on its haunches, swayed in the support, leaned against the food box, rested its head on the food box and fell into a fitful sleep. From this it roused from time to time and always with the beginning of each stimulus with the exception of the light. All the responses had disappeared within ten minutes of the injection, and sleep began, from which it was difficult to arouse the dog. The animal continued in a stuporous state through the next series of measurements, from 3:22 to 3:46 p. m., but by 6:03 p. m., when the third series was started, the responses were moderately

2. A supporting harness was sometimes used in the narcosis of the experiments with drugs.

strong, and the anmal was active and erect for five minutes following the sounding of the metronome (140 beats per minute). Again the effect was as though the animal had suddenly inhaled a noxious gas or had received a forceful blow on the head. Chart 2 shows a composite curve of the responses to the bell constructed by combining the results of experiments 1 and 2.

TABLE 6.—*Observations on the Effect of Sodium Iso-Amylethyl Barbiturate* *

		Control Salivary Production						
Stimulus		Minimum	Average	Maximum	March 29	March 30	March 31	General Reaction
Bell.....	R	180	222	290	233	226	204	Erect; quiet; quick movements
Metronome (140)	N	0	9	15	0	0	0	Slept
Bubbling sound.	R	180	231	290	280	233	282	Erect; quiet; quick movements
Metronome (60).	R	130	189	250	240	262	245	Erect; quiet; quick movements
Light (60).....	R	100	151	220	142	218	214	Erect; quiet; quick movements
Metronome (140)	N	0	11	15	0	0	0	Slept
Bell.....	R	140	200	240	†	†	313	Erect; quiet; quick movements

April 2, 1:55 p.m.: Sodium Iso-amylethyl Barbiturate, 375 mg. Intraperitoneally

			Latent Period†			
Time, P.M.	Stimulus		Secretory Response	Motor Response	Salivary Response	General Reaction
1:58	Bell.....	R	2	3	382.20	Overactive
2:00	Metronome (140)	N	—	—	0	Quiet
2:04	Bubbling sound.	R	—	—	14	Quiet
2:07	Metronome (60).	R	—	—	0	Unsteady; hanging head
2:10	Light (60).....	R	—	—	0	Unsteady; hanging head
2:13	Metronome (140)	N	9	—	31	Unsteady; hanging head; restless
2:17	Bell.....	R	5	—	9	Unsteady; hanging head; restless
3:22	Bell.....	R	5	—	80	Unsteady; stuporous; slept
3:25	Metronome (140)	N	—	—	0 (7)	Unsteady; stuporous; slept
3:30	Bubbling sound.	R	6	7	100	Unsteady; stuporous; slept
3:34	Metronome (60).	R	6	—	40	Unsteady; stuporous; slept
3:38	Light (60).....	R	—	—	0	Unsteady; stuporous; slept
3:42	Metronome (140)	N	—	—	0	Unsteady; stuporous; slept
3:46	Bell.....	R	7	—	82	Slept
6:03	Bell.....	R	4	5	182	Erect; quiet; quick movements
6:07	Metronome (140)	N	—	—	0	Slept
6:12	Bubbling sound.	R	6	7	132	Quiet; slow movements
6:17	Metronome (60).	R	5	7	146	Quiet; slow movements
6:21	Light (60).....	R	—	—	0	Slept
6:25	Metronome (140)	N	—	—	0	Slept
6:30	Bell.....	R	7	8	149	Erect; quiet; quick movements
A.M. April 3 (15 hours later)						
9:22	Bell.....	R	3	4	213	Erect; quiet; quick movements
9:27	Metronome (140)	N	—	—	0	Slept
9:32	Bubbling sound.	R	5	4	191	Erect; quiet; quick movements
9:38	Metronome (60).	R	4	—	193	Erect; quiet; quick movements
9:44	Light (60).....	R	7	—	118	Erect; quiet; quick movements
9:48	Metronome (140)	N	—	—	0	Slept
9:54	Bell.....	R	3	4	166	Erect; quiet; quick mevements

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

In the third experiment the results almost paralleled those obtained in the second. The only feature that was slightly different occurred in the responses during the first part of the narcotic phase when all the responses became about equal instead of ranging themselves quantitatively at a lower level in the order of their original strength.

In the fourth experiment a small and moderate dose of sodio-amyletheyl barbiturate, consisting of 7.5 mg. per kilogram, or a total of 0.1875 Gm., was given. The effect on the responses was far less marked. There was no appreciable

decrease in the salivary responses to the reenforced stimuli and only a slight reduction in the motor activity. However, the effect of the nonreenforced stimulus, (metronome, 140 beats per minute) was definitely greater. As was observed in the recovery after the larger dose was given, the sounding of the metronome at 140 beats per minute caused more pronounced changes than when the same stimulus was used during "control" experiments. Approximately four seconds after the stimulus had started the animal drooped as though suddenly overcome and remained in an unbroken sleep for five minutes, or until the ringing of the bell or the bubbling noise sounded. The sleep then promptly disappeared, and a typical response to the reenforced stimulus was elicited. No effect of the drug could be noted when the animal was observed outside the chamber.

The reaction time for both secretory and motor responses was shorter during the initial period of excitement, but after the onset of the narcotic phase the latency was prolonged. As the period of secondary increase in responses began the latency became shorter. In the experiments in which no such secondary increase occurred the reaction time gradually returned to the usual level.

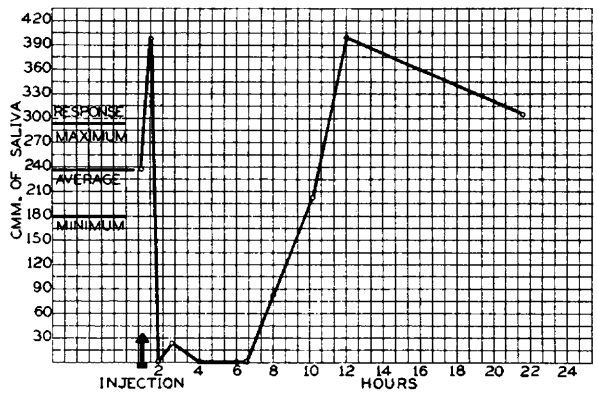

Chart 2.—Composite graphic representation of a series of experiments on the effect of sodium iso-amylethyl barbiturate on the conditioned response to the ringing of a bell. The drug was injected in a 10 per cent aqueous solution (time indicated by the arrow). For a few minutes after the injection the dog was overactive and gave an exaggerated salivary response to the conditioned stimuli. It then became more relaxed and lethargic, went to sleep and gave no appreciable salivary response to any of the stimuli for about five hours. At the end of ten hours the animal could be roused from its stupor and again became overactive, passing through another period of exaggerated responses. This overactive condition persisted for several hours. About ten hours after the dog's rousing from the lethargy the salivary response was still increased in amount over the maximum response observed during the control period.

The effects of sodium iso-amylethyl barbiturate on latency contrasted with those produced by caffeine sodiobenzoate. The caffeine sodiobenzoate shortened the latent period: In 80 per cent of the instances the interval between the stimulus and the onset of the reaction was one or two seconds. The barbiturate administered in moderate or large amounts, with the exceptions mentioned, caused the latency to be prolonged. In approximately 60 per cent of sixty-six observations the latent

period between the stimulus and the onset of the secretion was between eight and ten seconds (control experiment, 2 per cent).

Experiments with Sodium Bromide.—The effects of both small and large doses of sodium bromide were determined. The former were administered first. After the usual preparations for the measurement of saliva had been made, the dog was given an enema containing 120 mg. of sodium bromide per kilogram of body weight in 5 per cent aqueous solution, or a total of 3 Gm. (table 7). Nothing unusual was observed in the responses during the first twenty minutes following the administration of the drug. At the end of that time and after the presentation of the reenforced stimuli the movements became slightly slower; the animal rested its

TABLE 7.—*Observations on the Effect of Sodium Bromide* *

Stimulus		Control Salivary Production			May 25	May 26	General Reaction
		Minimum	Average	Maximum			
Bell	R	180	222	290	109	218	Alert
Metronome (140)	N	0	9	15	0	0	Slept
Bubbling sound	R	180	231	290	213	187	Alert
Metronome (60)	R	130	189	250	196	273	Alert
Light (60)	R	100	151	220	136	154	Alert
Metronome (140)	N	0	11	15	0	0	Slept
Bell	R	140	200	240	254	100	Alert

May 26, 3:05 p.m.: Sodium Bromide, 3 Gm. by Rectum

Time, P.M.	Stimulus		Latent Period†		Salivary Response	General Reaction
			Secretory Response	Motor Response		
3:09	Bell	R	2	3	218	Alert
3:14	Metronome (140)	N	—	—	0	Slept
3:19	Bubbling sound.	R	3	4	182	Slept; ate; slept
3:24	Metronome (60).	R	4	5	169	Slept; ate; slept
3:29	Light (60)	R	4	?	147	Slept; ate; slept
3:34	Metronome (140)	N	—	—	0	Slept
3:39	Bell	R	4	5	133	Alert
5:59	Bell	R	3	4	218	Alert
6:04	Metronome (140)	N	—	—	0	Slept
6:09	Bubbling sound.	R	2	3	227	Alert
6:14	Metronome (60).	R	4	5	173	Alert
6:19	Light (60)	R	3	—	146	Alert
6:24	Metronome (140)	N	—	—	0	Slept
6:28	Bell	R	3	4	223	Alert

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

head and even went to sleep for a minute and a half after the bubbling sound, the sound of a metronome beating 60 times per minute, and the flashing of the light, a reaction usually observed only after the sound of the metronome beating 140 times per minute. Four seconds after the presentation of the latter stimulus the dog showed the first evidence of stupor, which promptly progressed to a deep sleep. Uninterrupted sleep continued from 3:34 until 3:39 p. m., when the bell was sounded. At that time the movements were definitely slow, the orienting movements being slightly more continuous and the conditioned movements toward the food box delayed. The latent period between the onset of the ringing of the bell and the production of the first measurable amount of saliva was prolonged. (The average before the administration of the drug was two plus seconds; after the administration it was four plus seconds). The actual salivary production was reduced, although it remained within the average range.

The next series of measurements was begun at 5: 59 p. m., approximately three hours later. No deviation from the average was observed with the possible exception of the reaction to the metronome beating 140 times per minute. Both the speed of onset of sleep and its duration were slightly increased.

Large amounts of the drug were given in subsequent experiments. In an attempt to make the effect of the bromide more apparent, this type of experiment was postponed until an overactive state had spontaneously developed. This occurred in the later stages of the animal's pregnancy. After being prepared in the usual manner the dog was given an enema containing 280 mg. per kilogram (a total of 7 Gm.) of sodium bromide in 5 per cent aqueous solution. The effect was definite although the onset was slow.

The responses, both motor and salivary, were unusually high before the bromide was given. The animal moved about restlessly, whined, panted and pulled on the apparatus. The nonreenforced stimulus gave a response almost as strong as that produced by the flashing light. Besides there was considerable instability since the terminal ringing of the bell gave a response lower than the average response it had produced and out of line with the volume of the other responses. The bubbling sound and the metronome (60 beats per minute) both gave responses far larger than either the initial or the terminal bell.

The enema containing the bromide was given at 3: 52 p. m., and measurements made four and a half hours later showed that with one exception the responses to reenforced stimuli were all lowered. The nonreenforced stimulus (metronome, 140 beats per minute) elicited a very great response, 309 cu. mm., an amount in marked contrast to 45 cu. mm., the response to the terminal ringing of the bell. The weak and strong responses approximated each other, or the weak actually gave more than the strong.

During this series of measurements the motor activity was reduced considerably, although there was a recurrence of the initial restlessness and panting when the metronome beating 140 times per minutes was sounded, with the resultant secretion of 309 cu. mm. of saliva.

At 10: 07 p. m., or about six hours after the administration of bromide, the responses were again determined. Salivary response was elicited only by the strongest stimuli, the initial ringing of the bell, the bubbling sound and the metronome beating 60 times per minute, and even these responses were very small (although in the proper ratio), namely, 45, 45 and 27 cu. mm., respectively. The animal was sluggish and underactive throughout this period, but after the metronome beating 140 per minute was sounded the dog went into a stuporous sleep which was interrupted only long enough to eat the food that accompanied the presentation of subsequent stimuli.

Measurement made seventeen hours later showed that the responses were again greater than the average and that differentiation was poorly maintained.

A repetition of this experiment demonstrated that these results were not to be explained on the basis of the large dose of bromide alone. The following experiment was performed when the initial or control state of the animal was in no way unusual: Two grams of sodium bromide was given per rectum after a satisfactory preliminary period of control observation. The effect on the salivary and motor responses was similar to that in the first experiment. The duration of the action was somewhat longer, and the sleep after the sounding of the metronome with 140 beats per minute came on more promptly and persisted longer. There was more sleep from one to two minutes after the reenforced stimuli, but the differentiation was excellent, and the volume of the salivary responses to

reenforced stimuli was not decreased. No reversal or equalization of responses was noted.

Given in small doses the sodium bromide had little effect on the reaction time of either secretory or motor responses. Even with large doses the latency was usually within the range, although occasionally at the upper limits, of the average.

Experiments with Chloral Hydrate.—The animal was prepared for observation in the manner heretofore described and was then given an enema containing 100 mg. per kilogram, or 2.5 Gm., of chloral hydrate in 5 per cent aqueous solution. The first measurements were made seven minutes later and at three intervals during the next five hours (table 8).

TABLE 8.—*Observations on the Effect of Chloral Hydrate* *

Stimulus		Control Salivary Production: Minimum	Average	Maximum	June 2	General Reaction
Bell	R	180	222	290	118	Alert
Metronome (140)	N	0	9	15	18 (?)	Slept
Bubbling sound	R	180	231	290	182	Alert
Metronome (60)	R	130	189	250	220	Alert
Light (60)	R	100	151	220	138	Alert
Metronome (140)	N	0	11	15	13 (?)	Slept
Bell	R	140	200	240	291	Alert

June 2, 4:10 p.m.: Chloral Hydrate, 2.5 Gm. by Rectum

Time, P.M.	Stimulus		Latent Period†: Secretory Response	Motor Response	Salivary Response	General Reaction
4:17	Bell	R	?	?	282	Alert
4:22	Metronome	N	—	—	0 (9)	Slept
4:27	Bubbling sound.	R	3	4	155	Quiet
4:32	Metronome	R	2	3	200	Quiet; slept
4:37	Light	R	3	?	136	Quiet
4:42	Metronome	N	—	—	0 (13)	Slept
4:46	Bell	R	2	2	209	Alert
5:40	Bell	R	2	3	255	Alert
5:45	Metronome	N	—	—	0	Slept
5:50	Bubbling sound.	R	3	3	242	Quiet
5:55	Metronome	R	2	3	307	Quiet
6:00	Light	R	2	9	245	Quiet
6:05	Metronome	N	—	—	0	Slept
6:10	Bell	R	2	3	182	Alert

* The salivary production was measured in cubic millimeters. The same symbols are used as in table 1.

† In this column the minus sign indicates that no response occurred within ten seconds.

The results did not differ essentially from those observed following the administration of moderate amounts of sodium bromide or sodium iso-amylethyl barbiturate. The response to the stimuli was not reduced, and sometimes it was slightly raised. The contrast between the responses to reenforced and those to nonreenforced stimuli was accentuated. Sleep after the sounding of the metronome at 140 beats per minute was more promptly induced, less interrupted and of longer duration. There was occasional relaxation with half-closed eyes or sleep for one or two minutes after the reenforced stimuli, but this was superficial and frequently interrupted. The motor activity when the dog was within the chamber was slightly reduced. Before the administration of the drug the dog was erect, quiet and quick in movement with all the reenforced stimuli, and slow and relaxed with the nonreenforced stimuli; after the administration of the drug there was more relaxation throughout, with more resting of the head and far more sleep.

As with sodium bromide, no change in the general behavior of the animal when outside the chamber could be observed.

COMMENT

To indicate the effects of stimuli it is considered expedient to use the purely descriptive and neutral term "threshold." Thus, the phrase "threshold raising" indicates that for a variable period subsequent to the presentation of a given stimulus the salivary responses are reduced, and usually in association with this variation in response there are underactivity and relaxation with semiclosure of the eyes or sleep. Conversely, "threshold lowering" describes the effect of stimuli which are followed by an increase of salivary production, and when this occurs the dog becomes overactive and restless, pants, barks and whines.

In the preliminary analysis of the responses to the standard test stimuli it was noted that the reenforced stimuli, especially those involving stronger salivary responses, appeared to lower the threshold of the highest integrative function so that subsequent stimuli gave greater effects. On the other hand, after the establishment of a differentiation as the result of nonreenforcement of a stimulus, the presentation of that stimulus appeared to raise the threshold so that the responses to subsequent stimuli were less than when they had not been thus preceded. In fact, the rise in the threshold often became so great that the animal failed to respond not only to the reenforced stimuli but to all environmental stimuli and, in addition, seemed, to all outward appearances, to be asleep.

After the administration of caffeine sodiobenzoate the threshold was lowered. Differentiation was poorer during the period shortly after the injection, and apparently before there was much change in the responses to the reenforced stimuli. Furthermore, the sleeplessness is evidence that the nonreenforced stimuli were prevented from becoming as widespread in their effect on the behavior of the animal as was usual after the sounding of the metronome at 140 beats per minute. However, the general increase in the responses to the reenforced stimuli, both motor and salivary, was pronounced and appeared to parallel in time of onset and in degree that produced by the caffeine sodiobenzoate on the responses to nonreenforced stimuli.

The fact that in one experiment the response to the nonreenforced stimulus was greatly increased and that to the reenforced stimulus actually decreased is not to be taken as evidence that caffeine chiefly affects the reaction to the nonreenforced stimuli. A possible explanation for this unusual reaction is as follows: Within certain limits the response to a stimulus is in direct proportion to its intensity. When these limits are exceeded the reaction decreases. The effect of stimuli of tremendous intensity, such as great noises or flashes of light, may be not only to reduce the response to that stimulus but to disturb the reaction

to all subsequent stimuli (Pavlov [3]). Thus if, through administration of caffeine, the threshold is so lowered that the first bell has the effect of an excessively loud stimulus, the salivary response may be reduced. With this exception no decrease in the conditioned response was observed during any phase of the action of caffeine. (The observations recorded here essentially agree with those made by Nikiforovski [Pavlov [4]]).

The action of caffeine is further demonstrated in the course of long experiments in which the animal fails to maintain differences in the size of the acquired responses corresponding to stimuli of different strength. If the responses become weaker or equal and the animal becomes apathetic, the administration of caffeine promptly dispels the apathy, and the responses return to their usual and relative size (Pavlov [5]).

In short, the effect of caffeine on the highest integrative functions is general. The thresholds to both reenforced and nonreenforced conditioned stimuli are lowered to essentially the same degree. Caffeine has a prompt effect on the response to nonreenforced stimuli. It restricts their influence, since the usual let-down in general activity with or without sleep does not occur. Furthermore, it heightens the influence of the reenforced stimuli; that is, by lowering the threshold of the highest integrative functions, it accentuates the effect of threshold-lowering stimuli and lessens the effect of threshold-raising stimuli.

The action of the larger doses of sodium iso-amylethyl barbiturate may be divided into four phases: (1) the phase of initial increase in conditioned responses;[6] (2) the phase of narcosis; (3) the phase of recovery from narcosis, and (4) the phase of postnarcotic or secondary increase in conditioned responses. All the phases were not consistently present. The first phase was very short, owing perhaps to the rapid absorption through the peritoneum. The alteration in the salivary response might easily have been missed unless measurements were made within a few minutes after the injection. The last phase was possibly related to the duration of the narcotic phase. It was absent in the

3. Pavlov, I. P.: Conditioned Reflexes, translated by G. V. Anrep, New York, Oxford University Press, 1927, p. 318.

4. Pavlov,[3] p. 127.

5. Pavlov, I. P.: Lectures on Conditioned Reflexes, translated by W. H. Gantt, New York, International Publishing Co., 1928, p. 356.

6. In the course of anesthetizing several hundred cats for experimental purposes one of us (H. G. W.) observed that following the intraperitoneal injection of sodium iso-amylethyl barbiturate in doses of from 8 to 9 cc. of 1 per cent solution per kilogram of body weight, in the majority of instances the animal, if permitted, ran about, often bumping into obstacles, staggering, falling, and finally, when its legs failed to support it, lay on its side, and within from four to five minutes fell asleep.

experiments in which the narcotic phase was short and was present when the latter was long.

The size of the dose seemed to determine the degree of change in the responses as well as the duration of this change. Probably the rate of absorption of the drug is also a factor.

The initial increase in responses was not limited to the salivary response. The general motor overactivity was clearly apparent from the behavior of the dog.

The initial phase was followed by a second phase in which the threshold was so much higher that not even the strongest conditioned stimuli produced an effect, although the unconditioned stimuli still elicited a salivary response for a brief period. It is of interest that the orienting movements were present in a diminished form after both the conditioned and the unconditioned responses had disappeared. At the end of varying lengths of time the functions returned in the reverse order, namely, first the unconditioned responses, then the strongest conditioned responses, and last, the weakest conditioned responses.

The order of reduction or loss of conditioned responses, however, was not constant. In one instance the responses passed through different stages in which all became equal or the weaker actually became greater than the stronger. In addition, the response to the weakest nonreenforced stimulus became slightly greater than that to the weakest reenforced stimulus.

The experiment in which the action of a large dose of sodium bromide was superimposed on a state of initial irregularity in the size of the response better illustrates the variations through which a response may pass before it is ultimately extinguished. Even before the sodium bromide was given, the light (the weakest reenforced stimulus) elicited practically the same response as the terminal ringing of the bell, a relatively strong stimulus, whereas the metronome beating 140 times per minute, a stimulus usually followed by no salivary response, was now followed by the secretion of an amount nearly equal to that elicited by either of the reenforced stimuli.

Similar effects of the narcotics ethyl carbamate (urethane) and chloral hydrate have been described (Lebedinsky [7]). The reaction most commonly observed was a gradual weakening of all the conditioned responses, the weak conditioned stimuli becoming ineffective before the strong ones. However, this sequence is not constant. The several variations described—those (1) in which weak and strong stimuli elicit equal response, (2) in which weak stimuli elicit larger responses than strong stimuli, (3) in which the nonreenforced stimuli elicit greater responses than the reenforced and (4) in which none of the other

7. Lebedinsky, quoted by Pavlov,[3] p. 278.

stimuli elicits responses—may readily pass from one into the other. The order is variable, and no deviation may be considered as a specific reaction to a given narcotic, nonreenforced stimulus or other threshold-raising agent (Pavlov [8]).

These irregularities are best considered as various expressions of the same progressive influence which any threshold-raising process of sufficient intensity may have on the different manifestations of the highest integrative functions.

It has been generally recognized that for varying periods following the administration of narcotics there may be a phase of increased activity which precedes the stage of depression. For example, in lower vertebrates "increased reflex excitability," as measured by the patellar jerk and respiratory activity and by increases in the shortening and force of contraction of the skeletal, cardiac and smooth muscles, is described as present during exposure to dilute solutions of various narcotics, whereas corresponding decreases are seen with more concentrated solutions (Winterstein [9]). The explanation of this observation is still wanting, but there is evidence suggesting that the variations described may be related to the concentration of drugs in the immediate neighborhood of individual cells. For instance, certain plants, protozoa and leukocytes, when exposed to dilute solutions of narcotics, show an acceleration in the flow of protoplasm and in growth, motility and ciliary movements, all of which are retarded in higher concentrations of the same substances (Winterstein [9]). Determinations of metabolism made on isolated tissue indicate a similar acceleration of biologic activity, although caution must be exercised in the interpretation of the observations. Thus, the oxygen consumption of timothy grass bacilli (Bacillus Phlei) is raised in the presence of 0.3 per cent ethyl carbamate (urethane) or five hundredth-molar to five thousandth-molar potassium cyanide, while it is lowered in more concentrated solutions (Loebel, Richardson and Shorr [10]).

The "recovery" and "postnarcotic" overresponsive phase in the dogs may be compared to the late effects of sodium iso-amylethyl barbiturate in man. After intravenous injection of from 0.3 to 0.9 Gm., or from 4 to 13 mg. per kilogram of body weight, cataleptic or stuporous patients pass through a period of about two minutes during which they talk relatively freely. Then they relax into a stuporous sleep. After this sleep has persisted for from four to eight hours the patients occasionally become more responsive than before the induced sleep. During the

8. Pavlov,[3] p. 280.

9. Winterstein, Hans: Die Narcose, ed. 2, Berlin, Julius Springer, 1926.

10. Loebel, R. O.; Richardson, H. B., and Shorr, E.: The Respiratory Metabolism of Acid-Fast Bacteria as Influenced by Foodstuffs, Narcotics and Methylene Blue, J. Clin. Investigation **11**:839, 1932.

latter period of several hours they may walk about, feed themselves and respond to questions and to many of the usual environmental stimuli (Bleckwenn [11]). Analogous effects have been observed during the action of other agents, notably carbon dioxide and sodium cyanide (Loevenhart [12]).

Another clinical phenomenon, possibly allied to that under discussion, is the fact that convulsions occur in some patients who discontinue phenobarbital or bromides after a prolonged and continuous use. These persons, who have been free from convulsions for months, may have, following the sudden withdrawal of the drug, a series of attacks which surpass in severity and number those experienced before the drug was administered.

It is improbable that the barbiturates in general or any individual members of the group are the only drugs that give this "double-peaked" curve of conditioned responses. It is not uncommon to find a prolonged period of underresponsiveness from any cause followed by a period of overresponsiveness (Pavlov [13]).

The action of small doses of sodium iso-amylethyl barbiturate, sodium bromide and chloral hydrate can best be considered together. The administration of small amounts caused only slight changes in the behavior of the animal when outside the chamber. Even within the chamber the effect was observed chiefly during the action of the nonreenforced stimuli, although some slowing in movement and a resting of the head and occasionally sleep occurred after the reenforced stimuli. The effect on the response to the nonreenforced stimuli was definite. Within from four to five seconds of the onset of the stimulus the dog was apparently deeply asleep and remained so during the full period between the stimuli. When the next reenforced stimulus sounded the animal immediately awoke, with the usual quick and brief orienting movements, which were followed by prompt conditioned movements and salivary response. There was an occasional delay in the onset of the conditioned movements and salivary response with a reduction in the volume of the salivary production, and the erect posture, quick movements and wakefulness were short-lived. After a minute or two the animal usually rested against the supports and seemingly slept.

Thus, even after small doses of the drugs the threshold became higher. This was particularly evident in the change of the response to

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11. Bleckwenn, W. J.: The Use of Sodium Amytal in Catatonia, in Schizophrenia (Dementia Praecox), A. Research Nerv. & Ment. Dis., Proc. **10**:224, 1931.

12. Loevenhart, A. S.; Lorenz, W. F.; Martin, H. G., and Malone, J. Y.: Stimulation of the Respiration by Sodium Cyanide and Its Clinical Application, Arch. Int. Med. **21**:109 (Jan.) 1918. Loevenhart, A. S.; Lorenz, W. F., and Waters, R. M.: Cerebral Stimulation, J. A. M. A. **92**:880 (March 16) 1929.

13. Pavlov,[3] p. 399.

the nonreenforced stimuli. Unlike caffeine sodiobenzoate, which dispelled sleep, these drugs seemed to facilitate its induction. The effect of the nonreenforced stimulus was augmented. The prompt relaxation and onset of sleep suggest that the effect on the threshold was diffuse, although the contrast between the responses to reenforced and those to nonreenforced stimuli was not reduced. In fact, with few exceptions the salivary responses to the reenforced stimuli after a small dose were well within the range of the control measurements and, on one occasion, were even greater than was usual.

The observations described in this report essentially agree with those made in Pavlov's laboratory.[14] A dog in which the responses had become irregular and weak was given 100 cc. of a 2 per cent solution of potassium bromide by rectum. At the end of ten days all the responses had returned to their usual and relative size. No reduction in the magnitude of the reenforced stimuli was observed as a result of the administration of the drug. In another of Pavlov's experiments the rectal administration of potassium bromide restored normal function in a dog in which irregular and weak responses had developed as the result of a difficult differentiation. In this dog the "strength of the positive conditioned action was not decreased but was even somewhat augmented" (Pavlov[15]).

The results of our experiments lend themselves to a slightly different interpretation. In the first place, it is clear that when bromide, chloral hydrate or sodium iso-amylethyl barbiturate is given in large doses it raises the threshold to both reenforced and nonreenforced stimuli. Only when the amount given is small or moderate is a degree of differential action noted. It is more in accordance with the observations to say that when small or moderate amounts of these drugs are administered the earliest effect is an increase in the influence of the nonreenforced stimuli. This is shown specifically not only in the complete absence of salivary responses when the nonreenforced stimulus is presented but more generally in the reduced motor activity, relaxation and sleep that follow these threshold-raising stimuli. The only perceptible effect on the responses to the reenforced stimuli is to delimit more strictly the influence of the latter to the salivary response and to hinder the extension of their threshold-lowering influence to the other functions. This curtailing effect is especially evident in the short-lived and decreased motor activity. To summarize, small or moderate amounts of these drugs, by raising the threshold of the highest integrative functions, accentuate first the effect of the threshold-raising stimuli. In addition they lessen the effect of the threshold-lowering stimuli.

14. Pavlov,[3] p. 300.

15. Pavlov,[5] p. 343.

THEORY

The Interaction of Threshold-Altering Processes.—The evidence presented justifies the inference that chemical substances which alter the threshold of the highest integrative functions are not essentially different in their effect from other threshold-altering processes. The interaction of the effects arising from drugs and conditioned stimuli does not permit precise mathematical expression, but rough measurements indicate that in combination the effects may be expressed as an algebraic summation.

The effect of a threshold-raising stimulus presented when the threshold is already raised owing to the administration of bromide is to add to the already high level, raising it still higher. Should the threshold be initially lowered owing to the action of caffeine, the effect of a threshold-lowering stimulus summates with the effect of the drug, depressing the threshold still further. Conversely, should the threshold be raised by the administration of bromide, the effect of a threshold-lowering stimulus would be reduced, and the amount of reduction would be dependent on the strength of its effect as compared to that of the bromide. In other words, a stimulus in altering the threshold does so on the basis of the already existent level and not alone by virtue of its inherent physical nature.

These considerations emphasize the futility of attempting to classify effects involving the highest integrative functions according to the origin of stimuli or the nature of the factors which produce these effects. Every stimulus, complex of stimuli, or in general every change in the internal and external environment of the organism affects the threshold for subsequent stimuli.

In other words, the conditioned response is the resultant of a multitude of factors which have their origin in the entire experience of the organism and not merely in the part of its experience directly connected with the conditioning stimulus.

These fundamental theoretical considerations should prove useful in the attempt to understand the reactions of animals with more complex integrative functions than those of the dog. They indicate the necessity of properly evaluating the many factors in the genesis of psychobiologic reactions.

SUMMARY AND CONCLUSIONS

1. The highest integrative functions were studied and quantitatively expressed in terms of one of the measurable components of the dog's "acquired" or "conditioned" responses to standard stimuli.

2. For the purposes of description the term "threshold-lowering stimulus" has been used to designate a stimulus which evokes a relatively strong response and which for a time increases the magnitude of the response to subsequent stimuli. The term "threshold-raising stimulus"

has been used to designate the stimulus which elicits little or no response and which for a time decreases the magnitude of the responses to subsequent stimuli. These terms are purely descriptive. They imply no knowledge of the anatomic or physiologic basis of the reactions they describe.

3. Caffeine sodiobenzoate lowers the threshold of the highest integrative functions. It accentuates the effect of the threshold-lowering stimuli and lessens the effect of the threshold-raising stimuli.

4. Small or moderate doses of sodium iso-amylethyl barbiturate, sodium bromide or chloral hydrate raise the threshold of the highest integrative functions. They accentuate primarily the effect of threshold-raising stimuli. In addition, they lessen the effect of threshold-lowering stimuli.

5. In larger doses the effect of sodium iso-amylethyl barbiturate may be divided into the following phases: (1) a brief phase during which conditioned responses are greater than the average, (2) the longer phase of narcosis, (3) the phase of recovery from narcosis and (4) (less constant) the postnarcotic phase during which the conditioned responses are again greater than during control periods.